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Ventricular assist device in severe heart failure

Effects on cytokines, complement and body weight

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Aims Inflammatory and immune activation and body wasting are important features of end-stage chronic heart failure. It is not known whether restoration of cardiac output by assist device implantation can improve these abnormalities.

Methods We studied 48 patients (39 males; age 45 ± 2 years) with NYHA class IV heart failure. All patients underwent ventricular assist device implantation for end-stage heart failure as a bridge to cardiac transplantation. Plasma levels of tumour necrosis factor α , and its receptors, interleukin-6, elastase, activated complement, and soluble CD14 receptors were measured at the time of operation and in survivors at 1 week ($n=46$), 40 days ($n=35$) and 90 days ($n=26$). Follow-up was for a minimum of 1 year.

Results One-year survival was 35% (95% CI: 22–49%). Body mass index was the only predictor of survival (body mass index >25 ($n=16$); survival 63 (39–86)%; body mass index <25 ($n=32$); survival 22 (7.5–36)%; $P=0.003$). Tumour necrosis factor α fell from 9.66 ± 1.33 pg \cdot ml⁻¹ to 4.2 ± 1.0 at 1 week ($P=0.008$), but returned to pre-operative levels at 90 days. Interleukin-6, activated complement and elastase fell progressively to 40 days, but were

rising at 90 days. There was no change in tumour necrosis factor receptor. There was a gradual rise in CD14 (3.99 ± 0.15 μ g \cdot ml⁻¹ at baseline, 5.02 ± 0.39 at 90 days, $P=0.006$). After surgery, body weight fell from 80 ± 2 to 73 ± 2 kg by 1 month ($P<0.001$) and to 72 ± 2 kg at 90 days.

Conclusions Ventricular assist device implantation results in a short-term fall in tumour necrosis factor α and interleukin-6, but no change in CD14 or tumour necrosis factor receptor, suggesting that the pathophysiological process resulting in inflammation was not altered by left ventricular assist device implantation. Low body mass index is related to poor outcome after assist device implantation, and no weight gain.

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Introduction

Key features of end-stage chronic heart failure are body wasting and inflammatory and immune activation. The origins of immune activation remain unclear, but may be related to body wasting, that is, cardiac cachexia^[1,2], itself associated with a particularly poor prognosis^[3].

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Possible explanations for immune activation include the heart as a source of cytokines, supported by the finding that explanted failing hearts exhibit tumour necrosis factor α expression^[4]. Transgenic mice with cardiac over-expression of tumour necrosis factor α develop impaired cardiac function, congestive heart failure and die prematurely^[4,5]. Thus, if the heart is, indeed, the origin of immune activation, it may contribute to further deterioration in cardiac function. The potential stimulus to cardiac production of tumour necrosis factor α is not clear.

Anker *et al.* have developed an alternative hypothesis, that immune activation may be secondary to bacterial

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endotoxin exposure, perhaps as a result of repeated episodes of bowel wall oedema and subsequent translocation of bacterial products across the intestinal wall^[7]. In support of this hypothesis, circulating levels of endotoxin are higher in heart failure patients with oedema, and become lower with diuretic treatment^[8].

We were interested to investigate what might happen to immune activation in a group of patients with very severe heart failure who had their central haemodynamic problem corrected by the implantation of a ventricular assist device. Device implantation is itself a potentially strongly immunogenic stimulus. We measured tumour necrosis factor α and its soluble receptor, and CD14 as a measure of endotoxin-cell interaction^[9]. In addition, we measured activated complement levels, and elastase as a measure of neutrophil activation^[10,11]. There is no treatment at present for cachexia in chronic heart failure patients that restores normal weight. To assess the global metabolic effects of left ventricular assist device implantation, we also studied body weight changes after surgery.

Methods

We studied 48 patients at a single site who had ventricular assist devices implanted for severe cardiac failure (all New York Heart Association class IV). The indication for device implantation was end-stage heart failure or cardiogenic shock in all cases. The underlying presumption in all cases was that the patient would die without further support whilst on maximal medical therapy. The aim for each patient was that device implantation would be a bridge to transplantation. The implantations were performed between November 1992 and June 1995.

The study was approved by the ethics Committee of the Berlin Charité Hospital. Many patients were unable to give consent for the blood testing, but a relative of the patient was asked to give consent where necessary.

An ELISA was used to measure both C3a (Progen Biotechnik GmbH, Heidelberg, Germany) and C5a (Behringwerke AG, Marburg, Germany), C3a and C5a being activated complement factors 3 and 5, respectively. Elastase was measured by a commercially available ELISA test (E. Merck AG, Darmstadt, Germany). CD14 was measured by an ELISA test kit with a sensitivity $1 \text{ ng} \cdot \text{ml}^{-1}$ (IBL, Hamburg, Germany). Test kits from R&D Systems (Minneapolis, MN, U.S.A.) were used to measure soluble tumour necrosis factor receptor 1 (sensitivity $25 \text{ pg} \cdot \text{ml}^{-1}$) and interleukin-6 (sensitivity $0.094 \text{ pg} \cdot \text{ml}^{-1}$). Total tumour necrosis factor α (Medgenix, Fleurus, Belgium; lower limit of detectability $3.0 \text{ pg} \cdot \text{ml}^{-1}$) was also measured. The results from this test are not influenced by soluble tumour necrosis factor receptors.

Samples were taken, separated and frozen at -80°C for later analysis. Plasma levels of the cytokines were measured. The same sampling system was used for all patients. Samples were taken at the time of surgery

Table 1 Pre-operative details of patients undergoing left ventricular assist device implantation

Patients (n=48)	
Sex	Males 39; females 9
Diagnosis	DCM 37; IHD 11
Age (years)	45.3 ± 2.0
Height (cm)	176.5 ± 1.3
Weight (kg)	76.2 ± 2.2
LVEF (%)	17.5 ± 0.7
Cardiac index ($\text{l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$)	1.73 ± 0.09
Heart rate (min^{-1})	123.1 ± 2.7
Mean systemic BP (mmHg)	66.5 ± 1.2
Mean pulmonary BP (mmHg)	35.9 ± 1.1

Patient data at time of implantation of ventricular assist device. DCM=dilated cardiomyopathy; IHD=ischemic heart disease; LVEF=left ventricular ejection fraction; BP=blood pressure. Figures given are mean (\pm SD).

(n=48), and in survivors at 1 week (n=46), 1 month (n=35) and 90 days (n=26) post-operation. Data for the cytokines measured were log transformed to achieve a normal distribution. We used Cox proportional hazard analysis with Kaplan-Meier plots to illustrate survival data. In those patients who survived at least 90 days (n=26), comparison between variables at different time slots was with a repeated measures analysis of variance, with post hoc analysis where appropriate. In order to compare data between the time slots for all subjects alive at that moment, repeated paired t-tests were used with statistical significance set at a probability of <0.01 . For other statistical tests, a probability of <0.05 was taken to be statistically significant. Correlations were performed by the least squares methods. Data are presented as mean \pm SD.

Results

Patient data at the time of surgery are shown in Table 1. There were more patients with dilated cardiomyopathy than with ischemic heart disease. All patients were on intravenous inotropic support at the time of implantation. The duration of heart failure before assist device implantation was 3.89 ± 3.94 years (range 1 month to 13 years). Twenty-five patients had a left ventricular assist device (20 patients had a NovacorTM, five a HeartMate TCITM) and 23 a biventricular assist (the Berlin HeartTM). The devices were implanted with the patient on cardiopulmonary bypass. Heparin was antagonized fully with protamine after termination of extracorporeal circulation. Intravenous heparin was started 6 to 12 h after the operation in the absence of bleeding. Patients with the Berlin Heart and Novacor were later switched to coumadine and acetylsalicylic acid was added. Patients on TCI received only acetylsalicylic acid. The HeartMate TCI left ventricular assist device implantation is distinct from the other two devices in that its

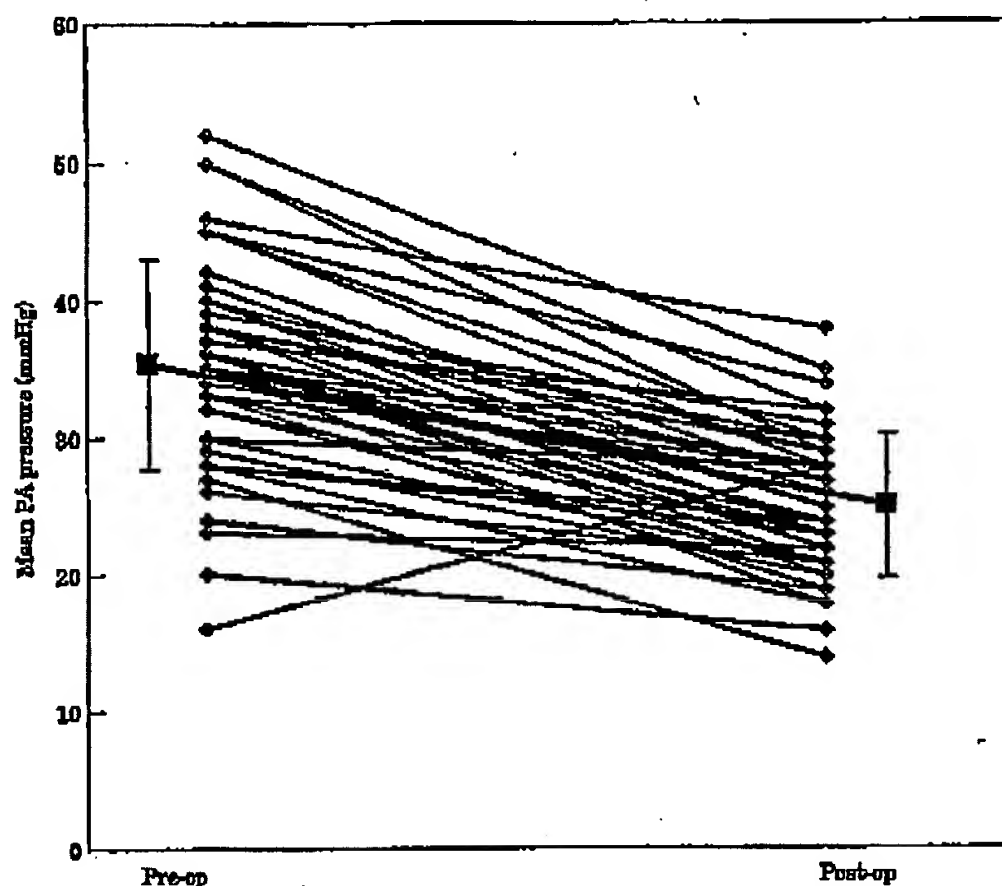


Figure 1 Mean pulmonary artery (PA) pressure immediately prior to the implantation of a ventricular support device and on return to the intensive care unit following the procedure.

pumping chamber is made of titanium and has a rough inner surface allowing for generation of an inner surface lining^[3].

The average age of the patients was 45.3 years (range 15.0–67.4 years). At operation, all patients were in the intensive care unit requiring isotropic support. Pulmonary artery pressure fell immediately after the operation from a mean of 35.3 ± 1.1 mmHg to 25.1 ± 0.8 ($P < 0.0001$) (Fig. 1). Mean systemic arterial pressure increased from 66.5 ± 1.2 at operation to 78.3 ± 1.3 at 1 week ($P < 0.0001$). There was no difference between devices in the haemodynamic response ($P > 0.2$).

The clinical outcomes are shown in Table 2. The mean duration of ventricular assist support was 124 days (range 3–796). Note that five subjects had sufficient recovery of ventricular function for their assist devices to be explanted, with long-term survival. These survivors all had a dilated cardiomyopathy, but had the same average age (45.0 ± 4.1 years), height (174 ± 4 cm) and cytokine levels as the main group. They had a higher cardiac index at implantation (2.1 l min^{-1} m^{-2}) than the main group, but ejection fraction and arterial pressures were the same. The survivors were heavier than the main group (85.2 ± 3.4 kg vs 75.2 ± 4.5 ; $P = 0.2$). The survival for the group as a whole is shown in Fig. 2.

The results for cytokine assays for all patients are shown in Table 3 and Fig. 3. There were no differences

between those who had a biventricular assist device implanted and those with a left ventricular assist. After device implantation, there was a significant initial fall in tumour necrosis factor α concentration, with a gradual return to pre-implantation values. In order to remove the bias induced by considering patients who died before the later stages of follow-up, we also show the data in Fig. 4 for those patients who survived with ventricular assist support for 90 days ($n = 26$). There was no substantial difference between the two sets of results. There was no difference in the measured cytokines at the time of

Table 2 Patient outcomes

Outcome	n	Time to transplant/ left ventricular assist device removal/death (range)
Death	31	99 ± 66 (3–378)
Transplant	12	101 ± 80 (10–247)
Transplant then death	5	71 ± 21 (39–91)
Survival	5	350 ± 259 (180–769)

Times are displayed in days. For the group who died following transplantation, the individual survival data following transplantation were 1 day, 2 days, 4 days, 19 days and 675 days. For those who survived, the time to removal of assist device is shown.

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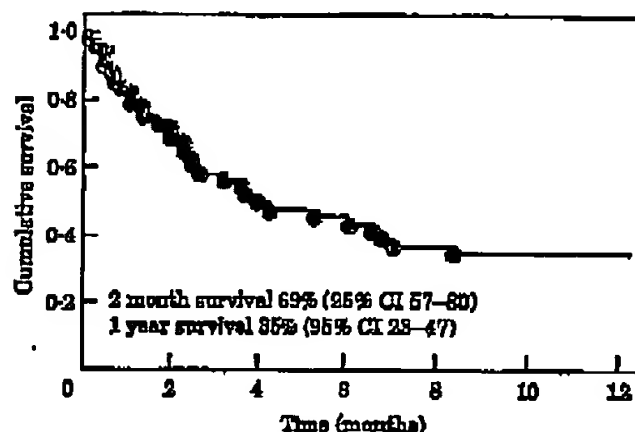


Figure 2 Kaplan-Meier survival curve showing times to first event. A first event is defined as death or transplantation. The data were censored at 1 year from assist device implantation.

operation between those who died during the first year of follow-up and those who survived ($n=12$). In Cox survival analyses, levels of the measured cytokines at operation did not predict outcome.

The rise in tumour necrosis factor α at 90 days follow-up was not associated with an increase in signs of infection. There was no rise in white cell count during this period (indeed, the white count fell slightly during follow-up; Table 3), and there was no correlation between the white cell count and tumour necrosis factor α at any time point. There was no interaction between the change in cytokine levels over time and clinical outcome (transplantation, death, survival).

There was no significant change in soluble tumour necrosis factor receptor type 1. There was a slight, but significant increase in soluble CD14 receptors over the time course of the study. Changes in elastase,

interleukin-6 and C3a paralleled the changes in tumour necrosis factor α , although the decline in these variables continued to the 40 day time point before beginning to rise again.

There was a reduction in body mass after the operation (79.6 ± 2.6 kg pre-operatively; 73.2 ± 2.4 at 1 month ($n=35$; $P<0.001$; Fig. 5), and 72.5 ± 2.6 at 90 days). There was a similar reduction in body mass index from 24.9 ± 0.8 kg \cdot m $^{-2}$ pre-operatively to 23.3 ± 0.5 kg \cdot m $^{-2}$ at 1 month ($P<0.001$ vs baseline) and 23.0 ± 0.8 kg \cdot m $^{-2}$ at 90 days ($P>0.2$ for the comparison with 1 month). This difference was more marked when the mass of the devices was subtracted from the patients' weight (72.4 ± 14.3 kg at 1 month, 71.7 ± 14.3 at 90 days). There was no relation between body mass index and duration of heart failure ($R=0.03$; $P>0.5$).

Survival analysis

Those patients who survived 90 days following the operation ($n=26$) were heavier at the time of operation than those who died (83.1 (15.3) kg vs 73.4 (10.5); $P=0.008$). Pre-operative body mass index predicted survival as a continuous variable ($P=0.0053$). Figure 6 shows survival in patients with a body mass index above and below 25 kg \cdot m $^{-2}$, which was the cut off for the group of patients in the highest tertile for body mass index.

Of the cytokines measured at baseline, only tumour necrosis factor receptor-1 weakly predicted survival ($P=0.02$). Urea also predicted outcome ($P=0.01$). There was no effect from electrolytes, blood count variables or liver function on survival. There was no effect from sex, age or underlying cause of heart failure on outcome. Only body mass index was an independent predictor of survival.

Table 3 Change in lumoral variables from implantation of assist device in chronic heart failure patients

	Pre-op ($n=48$)	1 week ($n=46$)	40 days ($n=35$)	90 days ($n=26$)
TNF α (pg \cdot ml $^{-1}$)	9.66 ± 1.33	4.20 ± 1.00	6.59 ± 1.42	7.84 ± 1.45
sTNFR-1 (pg \cdot ml $^{-1}$)	3201 ± 238	3578 ± 352	2700 ± 368	3478 ± 477
sCD14 (pg \cdot ml $^{-1}$)	9.99 ± 0.15	4.30 ± 0.22	4.18 ± 0.22	5.02 ± 0.39
C3a (ng \cdot ml $^{-1}$)	1082 ± 45	812 ± 46	657 ± 51	713 ± 69
Elastase (μ g \cdot ml $^{-1}$)	190.5 ± 14.3	90.2 ± 6.4	75.3 ± 7.6	77.9 ± 10.7
IL-6 (pg \cdot ml $^{-1}$)	131.3 ± 20.5	55.8 ± 17.3	21.4 ± 4.5	69.4 ± 46.0
C5a (ng \cdot ml $^{-1}$)	793 ± 161	992 ± 135	1130 ± 101	1106 ± 129
WCC ($\times 10^9 \cdot$ l $^{-1}$)	14.6 ± 0.8	14.8 ± 0.9	14.2 ± 1.4	11.4 ± 1.1
Hb (g \cdot l $^{-1}$)	106 ± 2	97 ± 2	97 ± 2	104 ± 3
Na $^+$ (mmol \cdot l $^{-1}$)	139.8 ± 0.7	138.4 ± 0.9	137.8 ± 0.8	137.5 ± 1.1
K $^+$ (mmol \cdot l $^{-1}$)	4.58 ± 0.07	4.44 ± 0.06	4.12 ± 0.07	4.20 ± 0.08
Urea (mmol \cdot l $^{-1}$)	29.7 ± 2.0	29.5 ± 2.4	18.3 ± 3.8	17.3 ± 2.5
Creatinine (μ mol \cdot l $^{-1}$)	165.0 ± 9.0	114.9 ± 9.4	99.5 ± 8.2	121.1 ± 9.8

Differential white cell counts are not available. TNF α =tumour necrosis factor α ; sTNFR-1=soluble tumour necrosis factor receptor type 1; sCD14=the soluble form of CD14; C3a and C5a=activated complement factors 3 and 5, respectively; IL-6=interleukin-6; WCC=white cell count; Hb=haemoglobin. The data are shown as means \pm SEM.

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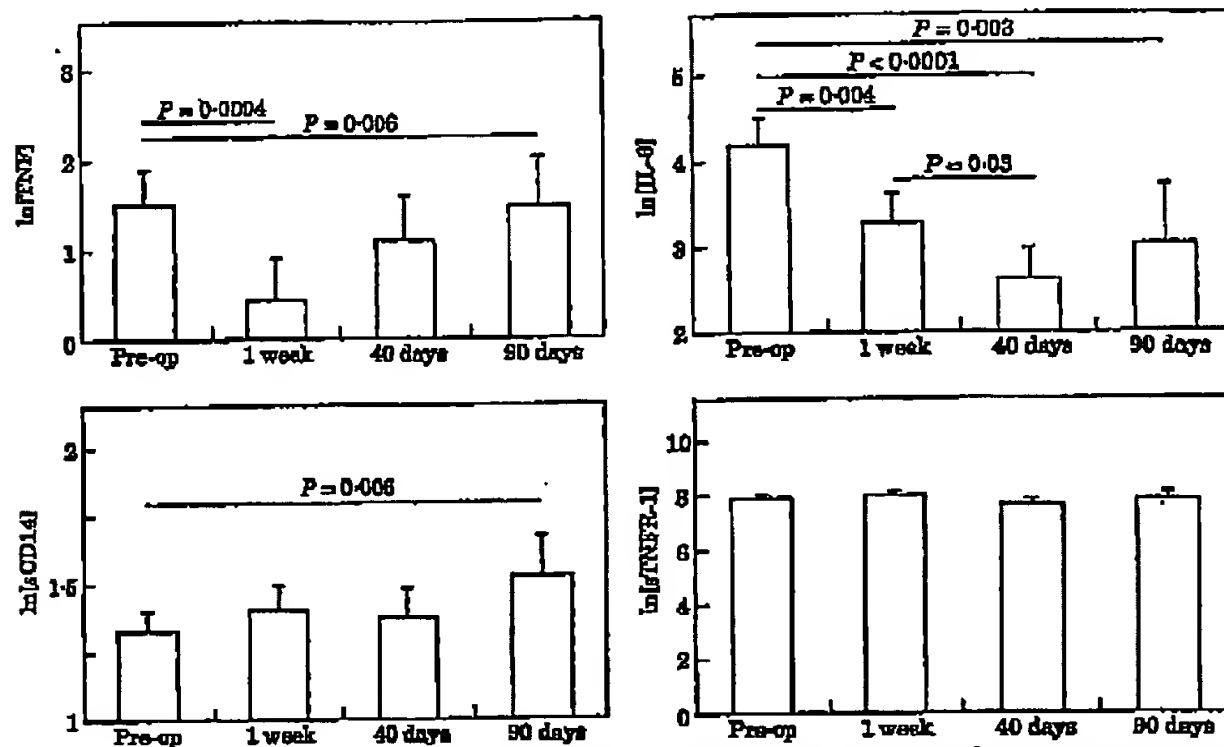


Figure 3 The behaviour of cytokine levels following device implantation. Natural logarithms of the data are shown as these were normally distributed. The error bars are the 95% confidence intervals.

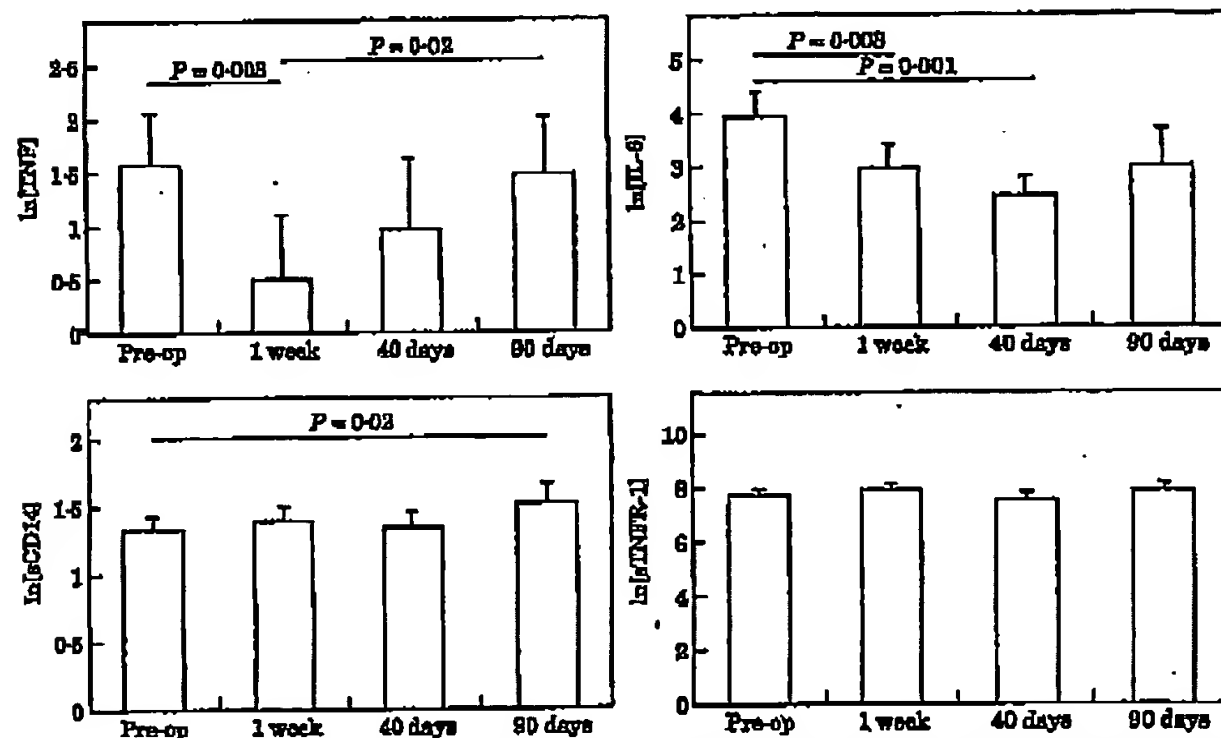


Figure 4 The behaviour of cytokine levels following device implantation. Natural logarithms of the data are shown as these were normally distributed. The error bars are the 95% confidence intervals. In this series of plots, data are shown only from those patients surviving until 90 days (n=26).

Correlation analysis

Correlations between variables are shown in Table 4. There was a close relationship between elastase and C3a

(Fig. 7). At the time of operation, there were no correlations between haemodynamic variables and any of the inflammatory indices measured. There was a close

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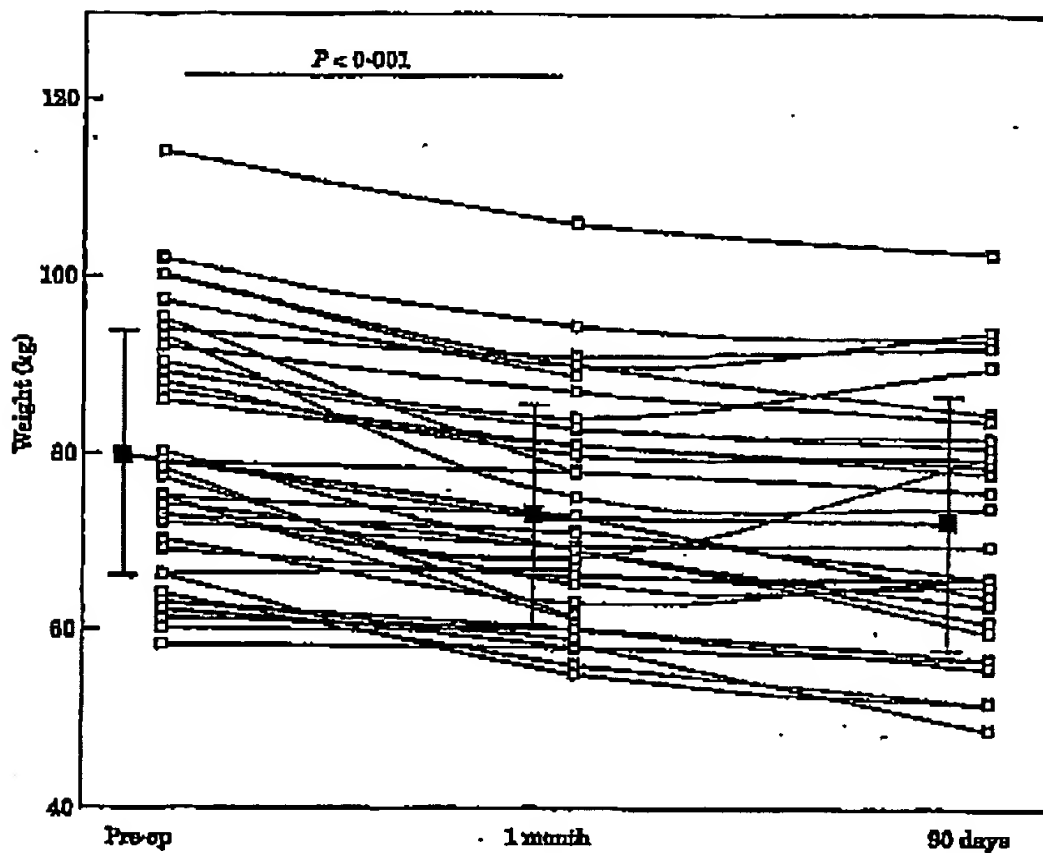


Figure 5 The pattern of weight loss in those patients surviving the first month of assist device implantation. The bolder lines represent two or more patients whose weight increased or decreased to the same level.

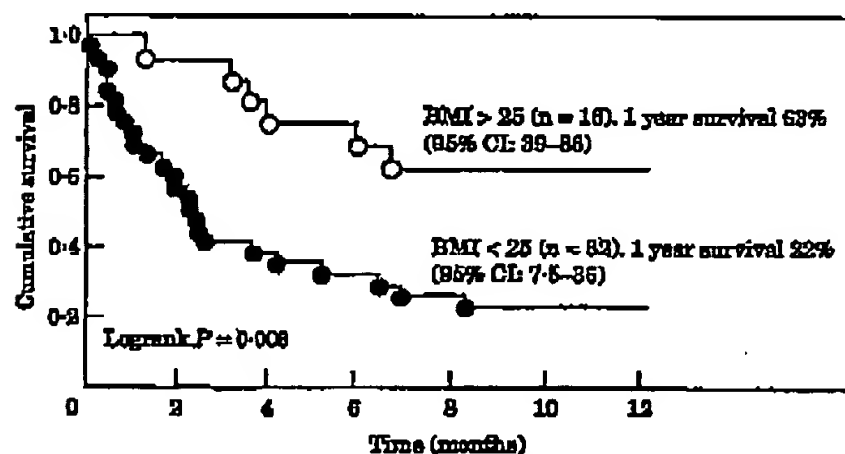


Figure 6 Survival in patients according to the body mass index (BMI) at time of assist device implantation.

relationship between urea and tumour necrosis factor receptor 1.

There was a very weak relationship between weight at operation and tumour necrosis factor receptor 1 ($r = -0.34$; $P < 0.05$), and between weight and interleukin-6 ($r = -0.37$; $P = 0.02$). There were no correlations between weight loss, expressed in absolute terms or as a proportion of initial weight, and change in

cytokine level, expressed in absolute terms or as a proportion of initial level.

Discussion

We have studied cytokine responses to the implantation of a left ventricular assist device in patients with

Table 4 Univariate correlation matrix for the inflammatory mediators measured

	ln[TNFR-1]	ln[TNF]	ln[sCD14]	ln[C3a]	ln[elastase]	ln[IL-6]	ln[C5a]	Urea
ln[TNF]	0.14							
ln[sCD14]	0.30	-0.11						
ln[C3a]	0.23	-0.03	0.06					
ln[elastase]	0.32	0.02	0.08	0.82 (<0.001)				
ln[IL-6]	0.35	-0.07	0.04	0.40 (<0.001)	0.40 (<0.001)			
ln[C5a]	0.32	-0.1	0.48 (<0.001)	0.02	0.12	-0.15		
Urea	0.63 ($P<0.001$)	0.26	0.25	0.12	0.16	0.17	-0.05	
WCC	0.003	0.22	0.21	0.33	0.35	0.006	-0.07	-0.05

Results are shown for data at the time of operation ($n=48$). TNFR-1=tumour necrosis factor receptor type 1; TNF=tumour necrosis factor; sCD14=soluble CD14; C3a and C5a=activated complement factors 3 and 5, respectively; IL-6=interleukin-6; WCC=white cell count.

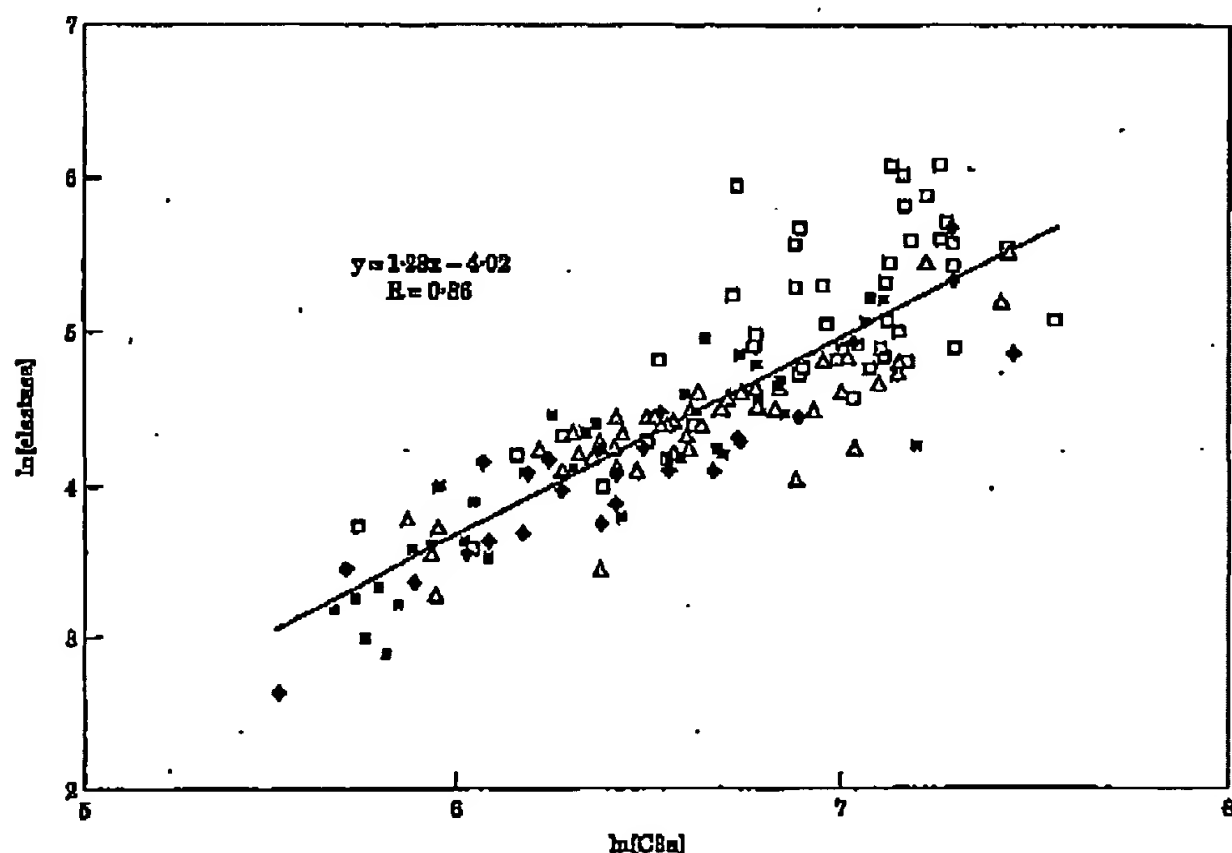


Figure 7 The relationship between elastase and activated C3. ■=before operation; Δ=1 week; ■=40 days; ◆=90 days.

end-stage heart failure. Device implantation results in a temporary fall in tumour necrosis factor α and interleukin-6, but these largely returned to pre-implantation levels by 90 days follow-up. Although none of the cytokines we measured independently predicted outcome, there was a strong relationship between body mass at the time of operation and clinical outcome.

Elevated levels of tumour necrosis α were first reported in 1990 by Levine *et al.* who studied heart failure patients

with cachexia^[1]. Many other immune cytokines have been reported to be elevated in chronic heart failure, such as interleukins 1^[15], 2^[15,16], 6^[17] and 8^[18], soluble tumour necrosis factor receptors^[7,19], and leukocyte chemokines^[20]. Associated with the immune activation is a generalized imbalance between anabolic and catabolic processes^[21,22], such that catabolism predominates^[23].

There are two complementary explanations for the origin of these phenomena. One asserts that abnormal